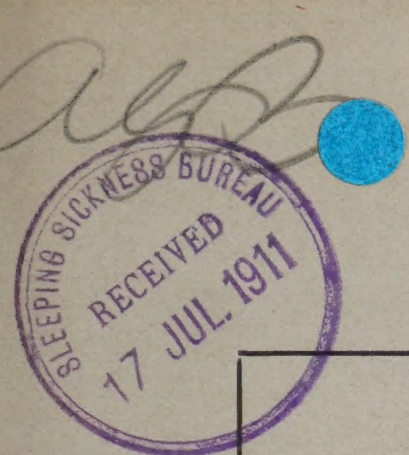




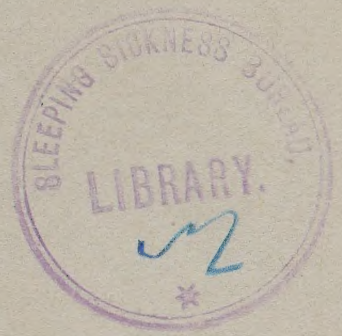
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The Duration of Trypanosome Infections

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I. INTRODUCTION

It is well known that trypanosomes may be absent for long periods from the peripheral blood of an animal or of a person suffering from an infection by trypanosomes, and that although no treatment has been given. It also frequently happens that the parasites may reappear, after a more or less lengthy absence, in the blood of persons or of animals who have apparently been cured by appropriate treatment of an infection by trypanosomes. It is important to collect instances of such disappearances and recurrences of the parasites in order that an opinion may be formed as to the length of time during which a recurrence is possible in cases of apparent recovery from trypanosomiasis or apparent cure.

The following observations prove that symptoms may be absent for long periods from persons who are infected with trypanosomes, and that those infected may die from the disease many years after the date at which it was acquired.

One of five subjects of early trypanosomiasis in Africans who were seen in the Gambian Protectorate² during the winter of 1902, died from definite sleeping-sickness in 1905; the four other subjects were alive and well in May, 1904, but they were all dead, from unreported causes, in 1909.

The records of 102 infected persons who were seen in the Congo, at an early stage of their disease, when no symptoms beyond glandular enlargement were perceptible, indicate that one-third of such persons will live on without treatment for from thirty to forty months.³ It has not been possible to keep track of all of these negro patients, but five of them, without treatment, were well and working at forty-eight months after they were first observed to be infected.

The symptoms disappeared, without treatment, from three Europeans who were infected with trypanosomes; they recurred after ~~fifteen~~ months in one case

1. Nabarro, D.: Trypanosomes and Trypanosomiasis, transl. by Laveran and Mesnil, London, 1907, Ballière, Tindall & Cox, p. 370.

2. Dutton, J. E. and Todd, J. L.: First Report of the Trypanosomiasis Expedition to Senegambia (1902), Liverpool School of Tropical Medicine, Memoir XI, London, 1903, Williams and Norgate.

3. Todd, J. L.: A Review of the position of Gland Palpation in the Diagnosis of Human Trypanosomiasis. Jour. Trop. Med. and Hyg., London, 1908, xi, 229.

3 Todd J.L. The later history of cases of S.S. Arrived chad
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Gus XXXVII p 511.

and after three years in another. The third patient was still well two years after the commencement of the disease.⁴

A consideration of these facts makes it easy to understand why some observers hold that untreated human trypanosomiasis is, in the end, invariably fatal; while others believe that spontaneous recovery may occur, especially in localities such as the Gambia and Sierra Leone, where the disease is endemic and apparently less virulent than it is in areas where it is epidemic.

Before 1905, preparations of inorganic arsenic, especially liquor arsenicalis, were the most efficient trypanocides known. In 1905, the value of para-amido-phenyl-arsenic acid (atoxyl) was discovered. Since then other valuable trypanocides, such as the antimony preparations and various anilin compounds, have been described.

It was observed during the very earliest attempts at the treatment of trypanosomiasis, that the parasites frequently recurred and caused the death of animals which were supposed to have been cured.

The results have been published of the treatment of a large number of Europeans infected with trypanosomiasis; a number of these cases are mentioned in a recent number of the Bulletin of the Sleeping-Sickness Bureau.⁵ The history of several of these persons strongly indicates that recovery may occur in cases of trypanosomiasis if the patients be well cared for and efficiently treated. Many of these patients are in good health at more than three years after the commencement of their disease, while one is well nine years after the date on which symptoms were first observed.

Martin and Darré⁶ report four Europeans who were apparently cured out of twenty-two patients treated by atoxyl alone, or by atoxyl combined with orpiment or with tartar emetic; these four patients are in absolute health three and one-half to four years after the commencement of their disease.

Although the records of the treatment of these Europeans are so encouraging, the following facts should not be forgotten:

In some unfortunate instances, the disease has been entirely resistant to the therapeutic measures which have been successful in the treatment of other Europeans.

It has happened, not infrequently, that the trypanosomes have recurred and that the patients have died of trypanosomiasis in instances in which the disease was not treated early, or in which the treatment was not as energetic, or as constant, as it should have been. Even in patients who received early, energetic and constant treatment, signs of trypanosomiasis have been observed for so long as from three to five years after the commencement of the disease.^{5,6}

One patient, a European, who became infected in 1902 was treated and, in 1908, seemed to have been cured of the disease; in 1910 he died of it.⁷

4. Nattan-Larrier, L.: Sur les résultats du traitement de la trypanosomiase chez le blanc, Bull. Soc. de path. exotique, Paris, 1908, i, 620.

5. Todd, J. L.: Trypanosomiasis in Europeans, Bull. Sleeping-Sickness Bureau, London, 1910, ii, 314.

6. Martin, L. and Darré, H.: Résultats éloignés du traitement dans la trypanosomiase humaine, Bull. Soc. path. exotique, Paris, 1910, iii, 333.

7. Martin, L., and Darré, H.: Résultats éloignés du traitement dans la trypanosomiase humaine, Bull. Sleeping-Sickness Bureau, London, 1910, ii, 212.

Many Africans affected by trypanosomiasis have been treated by various methods. Unfortunately, careful records have not always been kept of the results of their treatment. The most important attempts at treatment on a large scale have been made since 1905. The commissions sent out by Great Britain, France, Portugal, Spain and Germany have all reported on the results of their attempts at treatment; while Broden and Rodhain at Léopoldville, Thiroux in Senegal, and Ayres Kopke at Lisbon, as well as other workers, have treated patients in smaller numbers. In spite of the warnings given by those who made the experiments and observations, which led to the employment of atoxyl and its derivatives in the treatment of trypanosomiasis, some of the investigators who have employed these trypanocides in the field have been carried away by the almost miraculous benefit which they bring to persons even moribund from sleeping-sickness: consequently, unduly favorable reports have sometimes been made concerning these drugs. Yet, although the records have not been published of even a small proportion of the patients treated by these commissions and workers, it does seem probable, from the reports which have been published, that a proportion of the negroes treated have been cured of the disease.

Hodges⁸ reviews the results of the treatment of several hundred cases in Uganda since 1906. He concludes that the percentage of apparent cures is extremely small (about 2 per cent. of the total number of patients treated at all stages of the disease). The probability of the treatment being successful depends upon the earliness with which it is commenced; and the number of recurrences increases with the length of time elapsed since the discontinuance of the treatment.

The cases are reported of two sick sepoys who were apparently cured five years after they were found to be infected.⁸

A negro,⁹ who seemed to be cured of trypanosomiasis, had a recurrence of the disease after fifteen months of, apparently, perfect health.

Kopke¹⁰ reports the results obtained in 52 cases of trypanosomiasis in Africans, who were treated by him since July, 1905; atoxyl was given alone, or in combination with other drugs. Six of the patients are possibly cured; the trypanosomes have been absent, without a recurrence, from the blood of one of them for two and a half years. It seemed practically impossible to cure patients whose cerebrospinal fluid contained trypanosomes; thirty-four such patients died within a year after the commencement of treatment.

The records of these last cases tend to support the assertion that the appearance of the third stage of sleeping-sickness and of its accompany-

8. Hodges, A.: Progress Report on the Uganda Sleeping-Sickness Camps from December, 1906, to November, 1909, Bull. Sleeping-Sickness Bureau, London, 1910, xix, 260.

9. Martin, G., and Leboeuf: Les rechutes dans le traitement de la trypanosomiase humaine; De l'association de la couleur de benzidine Ph. (Afridol violet) à l'atoxyl. Bull. Soc. pathol. exotique, Paris, 1909, ii, 54.

10. Kopke, A.: Traitement de la trypanosomiase humaine; Rapport présenté au XVI Congrès International de Médecine, Trav. de l'Ecole de méd. trop. de Lisbonne, Lisbonne, 1909.

ing symptoms is caused by the penetration of the trypanosomes into the cerebrospinal canal. It also supports the assertion that patients whose cerebrospinal fluid contains trypanosomes invariably die, and that it is useless to attempt to treat them.

The following case is of interest in this connection. Its chief interest is that it scarcely agrees with the above assertions, since symptoms of nervous derangement were never present and the patient lived, in spite of very inadequate treatment, for four years and seven months after trypanosomes were found in his cerebrospinal fluid.

The patient, a male negro, aged 23, seen July 7, 1904, lived in the missionary station at Bolobo. He had been ill for a year and had lost a little weight; he complained of weakness and there had been intermittent insomnia and headache; no change had been noticed in his character and there had been no pathologic sleep.

The patient was well nourished and muscular. A careful physical examination disclosed nothing abnormal save a spleen which extended 10 c.c. below the costal margin. When the sole of the foot was stroked the great toe was extended. The pulse-rate was 84 and the temperature was normal. The glands were not definitely enlarged.

Trypanosomes were not found in the blood; the cerebrospinal fluid was distinctly cloudy and on examination was found to contain a few trypanosomes together with scanty leukocytes.

A short course of liquor arsenicalis was commenced at once; no record was kept of the way in which it was administered but it was not given constantly. After that time the patient, occasionally, had slight fevers. On Feb. 6, 1909, trypanosomes could not be found in the blood but the patient was not as strong as he had been and his friends feared that he had sleeping-sickness.

III. TRYPANOSOMIASIS IN ANIMALS

Each of the trypanosomes which cause a disease in animals has been shown to be pathogenic for every mammal into which it has been sub-inoculated. It is true that the intensity of the infection produced varies in accordance with the virulence of the parasite and with the susceptibility of the animal inoculated.

For example, *Trypanosoma gambiense* produces a severe infection in some monkeys, (*Cercopithecus patas*), while baboons are almost resistant to it.

The virulence of the infection produced by each parasite in the experimental animal employed is usually constant.

For example, *Trypanosoma brucei* always kills rats and other small animals quickly, but the disease produced by it in cattle may last for, certainly, several months.

Trypanosoma dimorphon always kills small laboratory animals rather less quickly than does *Trypanosoma brucei*, while cattle infected by it may live in perfect health for several years.

Although the type of infection produced by each trypanosome in each experimental animal is more or less constant, yet exceptions do occur and an infection may run an unusually acute, or an unusually chronic course.

For example, rats and other small animals are easily infected with *Trypanosoma gambiense* and they usually die of the infection within a month or two;¹¹ but an infection has been observed to last in a rat for 388 days and infected animals occasionally recover.¹²

Monkeys, infected with *Trypanosoma gambiense*, have remained for 150 days without showing symptoms of the disease.

Trypanosoma dimorphon usually kills horses infected by it; but the disease caused by it sometimes runs a chronic course and horses may even recover as in the following instance.

A horse, Case VI,² found naturally infected with *Trypanosoma dimorphon* in the Gambia in 1902, and brought to England; it was carefully observed until January, 1907. Then, since the animal had always been in apparently excellent health and since its blood was never found to be infected with trypanosomes, in spite of the most careful examinations, it was thought to be cured. The horse was reinoculated in February, 1907, and again in July with *Trypanosoma dimorphon*, in order to ascertain whether an immunity had been acquired. The animal sickened; trypanosomes were constantly in its blood, and in spite of treatment with antimony, it died a year later of trypanosomiasis.

Another horse, Case X,² observed to be infected at the same time, remained in the Gambia. It was still alive and well in February, 1909. Subject VI was not treated; Subject X, which remained in the Gambia, received liquor arsenicalis from time to time and it was well cared for although it was constantly worked.

Many attempts have been made in animals of various species to treat natural and artificially produced infections of many different trypanosomes. Because *Trypanosoma brucei* produces a disease of short duration and of constant type in experimental animals, it has been used most frequently in these attempts.

Because of the absolute control under which they are treated and because of the large doses of trypanocidal drugs which they tolerate, a large number of animals, especially laboratory animals, have certainly been cured of experimental infections by the parasites of nagana and of other trypanosomiasis.

Many rats cured of nagana, by various methods, have lived uninfected, for from 200 to 519 days after the cessation of treatment.

Monkeys treated by atoxyl and mercury for an experimental infection with *Trypanosoma gambiense* have remained healthy for over a year.¹³

Much caution should be used, however, before an animal is accepted as cured; for it has frequently happened that trypanosomes have recurred after an exceedingly long period and have led to the death of an apparently cured animal.

11. Dutton, J. E., Todd, J. L., and Kinghorn, A.: Cattle Trypanosomiasis in the Congo Free State, Ann. Trop. Med. and Parasit., Liverpool, 1907, ii, 233.

12. Thomas, H. W., and Linton, S. F.: A Comparison of the Animal Reactions of the Trypanosomes of Uganda and the Congo Free State Sleeping-Sickness, with those of *Trypanosoma gambiense*, Liverpool School Trop. Med., Memoir xiii, London, 1904, Williams and Norgate. *h. 76.*

13. Breinl, A.: Experiments on the Combined Atoxyl-Mercury Treatment in Monkeys Infected with *Trypanosoma gambiense*, Ann. Trop. Med. and Parasit., Liverpool, 1909, ii, 345.

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A rat died of an infection by *Trypanosoma brucei*; the parasites had appeared in its blood 222 days after they had been driven from it by a dose of atoxyl.¹⁴ Recurrences after about 100 days are frequently recorded: *Trypanosoma brucei* reappeared, for the third time, in the blood of a rat which had been treated by arsenophenylglycin¹⁵ after an interval of 148 days. Another dose of the drug caused the parasites to disappear; they are still absent 264 days later.

Trypanosoma equiperdum reappeared after intervals of 105 to 126 days in the blood of rats treated by orsudan,¹⁶ a preparation similar to atoxyl.

IV. CONCLUSIONS

The good results which followed the treatment of human trypanosomiasis usually have been so immediate and the patients have remained in good health so long, that it seems exceedingly probable that some can be cured; but it is evident, from a consideration of the records of patients treated that, to be successful, the treatment must be energetic and must commence early in the course of the disease. Since the disease has recurred after eight years in persons who had apparently recovered from it, or had been apparently cured of it, it is evident that it would be rash, with our present knowledge, to state definitely that a patient is cured, until that length of time has elapsed since the commencement of treatment. During that period, the case should be carefully observed in order to recognize and combat any recurrence. Similar conclusions may be drawn from the records of the treatment of animal trypanosomiasis.

NOTE.—In addition to the authorities previously cited, the following will be found of interest:

Bruce, D.: Further Report on the Tsetse-Fly Disease or Nagana in Zululand, London, 1897, Harrison & Sons.

Thomas, H. W. and Breinl, A.: Trypanosomes, trypanosomiasis and sleeping-sickness, Liverpool School Trop. Med., Memoir XVI, London, 1905, Williams and Norgate.

14. Moore, B., Nierenstein, M., and Todd, J. L.: The Treatment of Experimental Trypanosomiasis, Part II, Ann. Trop. Med. and Parasit., Liverpool, 1908, 265.

15. Campbell, R. P., and Todd, J. L.: The Action of Arsenophenylglycin on *Trypanosoma brucei*. Montreal Med. Jour., 1909, xxxviii, 794.

16. Kinghorn, A., and Montgomery, R. E.: Human Trypanosomiasis in Rhodesia and Nyasaland, Ann. Trop. Med. and Parasit., Liverpool, 1909, ii, 277.



Biochemical & Therapeutical Studies etc.

16. Breinl & Nierenstein. Ann. Trop. Med. 1909. iii p. 395

